Pd-Catalyzed Asymmetric Allylic C-H Functionalization

Pu-Sheng Wang[1] and Liuzhu' Gong[1]

[1]University of Science and Technology of China

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Abstract

Pd-catalyzed asymmetric allylic C-H functionalization has emerged as a powerful tool to access chiral, densely functionalized molecules from easily ac-cessible alkenes, enabling the increase of the step- or atom-economy by minimizing functional group manipulations for preparing allylating reagents. Due to the inadequacy of stereoselection strategies, the asymmetric allylic C-H functionalization is still in the early stage. In this essay, we will describe our journey to identification of asymmetric catalytic systems, mechanism of allylic C-H activation, control of stereo- and regioselectivity, and applica-tions in asymmetric synthesis.

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Pd-Catalyzed Asymmetric Allylic C-H Functionalization

Pu-Sheng Wang,[a] and Liu-Zhu Gong*[,a,b]

[a] Department of Chemistry, University of Science and Technology of China, Hefei 230026, China[b] Center for Excellence in Molecular Synthesis of CAS, University of Science and Technology of China, Hefei 230026, China

Interview **Question 1?** Answer 1. Interview Question 2? Answer 2. Interview Question 3? Answer 3. Interview Question

Comprehensive Summary

Pd-catalyzed asymmetric allylic C-H functionalization has emerged as a powerful tool to access chiral, densely functionalize

Keywords

Allylic C-H functionalization| palladium catalysis |cooperative catalysis | allylic substitution | asymmetric catalysis

Pu-Sheng Wang (left) was born in 1988 in Anhui, China. He received
Liu-Zhu Gong (right) was born in October 1970 in Henan, China. He g

Left to Right: Pu-Sheng Wang, Liu-Zhu Gong

Contents

1. Introduction

Pd-catalyzed asymmetric allylic substitutions,[1]featuring abundantly available chiral ligands, diverse bond-forming capacity and good functionality tolerance, are synthetically useful transformations[2] to convert allylating reagents to chiral allylic molecules (Scheme 1), and have exerted historical impact on synthetic organic chemistry. However, pre-preparation of active allylating reagents (e.g. allylic carbonates and allylic carboxylates) is basically required for this type of reaction to unavoidably necessitate additional work-up procedures. As a result, either the step- or atom-economy of the entire process is to some degree impaired. Alternatively, allylic C-H functionalization of olefins has long been a solution of great interest to directly provide allylic compounds by minimizing functionality manipulations for preparing allylating reagents.[3] Pd-catalyzed allylic C-H activation generally occurs with highly electrophilic Pd(II) catalysts under harsh conditions (Scheme 1). However, the presence of common chiral ligands containing phosphorus or nitrogen donor atoms principally deactivates the Pd(II) catalysts or causes incompatibility issues with oxidizing conditions.[4] Over the past few decades, Pd-catalyzed asymmetric allylic C-H functionalization has evolved rather slowly, presumably arising from the inadequacy of stereochemical control strategies.[5] In combination with a chiral Lewis acid, White and co-workers established an asymmetric allylic C-H esterification,[6]wherein the interaction of chiral Lewis acid co-catalyst with π-allyl-Pd intermediate is supposed to impart the stereochemical outcome. Although only moderate levels of enantioselectivity are obtained, it still represents a ground-breaking example. Unfortunately, no follow-up reports appear on other bond-forming reactions. Landmark work reported by Trost and co-workers demonstrates that trivalent phosphorus derivatives are promising ligands to promote Pd-catalyzed allylic C-H functionalization.[7] More importantly, chiral phosphoramidite ligands derived from (*S*)-BINOL are able to control enantioselectivity, culminating in the first Pd-catalyzed asymmetric allylic C-H alkylation of allylarenes with cyclic 1,3-diketones.[8]

Scheme 1 Pd-catalyzed asymmetric allylic substitution

Our research interest in this area stemmed from the experience in asymmetric organo/transition-metal combined catalysis (AOMC),[9] which has grown to be a general concept for the synergistically or sequentially integrating bond-breaking and bond-forming events to stereoselectively build up molecular complexity. Inspired by the successful examples of asymmetric allylic alkylation reactions rendered by chiral enamine/palladium cooperative catalysis,[10] we initially attempted to establish an asymmetric α-allylation of ketones or aldehydes with a-olefins by trapping the π-allyl-Pd intermediate with a chiral enamine.[5] Unfortunately, the use of chiral amines, even those capable of offering high enantioselectivity in Pd-catalyzed Tsuji-Trost type reactions, was unable to afford enantioselective allylic C-H alkylation reactions. Inspired by List's work on chiral counteranion directed α-allylation of aldehydes,[11] we successfully developed an asymmetric allylic C-H alkylation of allylarenes and 1,4-dienes with enolizable aldehydes (Scheme 2).[12]

Scheme 2 α-Allylation of aldehydes with olefins enabled by organo-metal cooperative catalysis

The initial success in asymmetric allylic C-H alkylation actually marked our starting point to deeply get involved in this field and prompted us to continuously endeavour to develop efficient catalyst systems, to understand the reaction mechanism and stereochemical control models, and to expand the applications in the enantioselective synthesis of natural products and pharmaceutically interesting molecules.

2. Allylic C-H Cleaving Mode: Concerted Proton and Two-Electron Transfer Process

Base-assisted proton abstraction has long been a widely accepted mechanism for Pd-catalyzed allylic C-H activation to generate π-allyl-Pd intermediate (Scheme 3),[13] and in most cases*p* -quinone derivatives are utilized as oxidants for Pd(II) catalyst regeneration from Pd(0).[14] Over our course of the study, the interaction between *p* -benzoquinone (BQ) and the Pd(0)-phosphine complex draws our attention to re-investigate the role of the *p* -quinone oxidant. Motivated by the early findings of the stable 16-electron [Pd(*p* -BQ)(PPh_3)$_2$][15]and [Pt(DQ)(CH_2=CH_2)(PCy_3)][16](DQ = duroquinone) complexes (Scheme 3), we speculated that a 16-electron Pd(0) complex bearing a trivalent phosphorus ligand, a*p* -quinone, and an alkene might be an active intermediate for allylic C-H cleavage. In collaboration with Hong group, a set of 16-electron metal complexes and C–H activation transition states (**TS-1**) for both Pd and Pt catalysis were computed to evaluate the feasibility of allylic C–H activation[17](Scheme 3). To our delight, the computational results suggest a concerted proton and two-electron transfer process to cleave the allylic C-H bonds, and the intrinsic low-energy barriers (14-21 kcal/mol) are in accordance with the experimental results, in which both Pd and Pt catalysis can allow a wide range of α-alkenes to undergo allylic C–H alkylation with soft carbon nucleophiles. Notably, in comparison with triarylphosphines, BINOL-based phosphoramidite ligands mostly exhibit superior performance in both the reaction conversion and the scope of carbon nucleophiles.[18]

Scheme 3 Pd-mediated allylic C-H activation

3. Stereochemical Control

Three general strategies were proposed to control the enantioselectivity of Pd-catalyzed allylic C-H functionalization[5](Scheme 4). The adoption of chiral organocatalysts in imparting stereoselection is our initial strategy, wherein chiral organocatalyst can interact with the nucleophile to stereoselectively direct the addition to π-allyl-Pd intermediate generated in situ from Pd-mediated cleavage of the allylic C-H bonds (Scheme 4a). Since either or both the ligand and organocatalyst can be chiral, this strategy provides more options to control the stereoselectivity. Chiral ligands always play a key role in the development of asymmetric metal-catalyzed reactions. Thus, bulky chiral phosphoramidite ligands were synthesized and evaluated for the Pd-catalyzed allylic C-H functionalization reactions (Scheme 4b).[19] These ligands, easily accessed from 3,3'-substituted BINOL/H_8-BINOL and amines, feature high structural flexibility and tunability to allow for the buildup of a large library of chiral phosphoramidites that are requisite for identification of the best chiral catalysts and rapid optimization of reaction conditions. Organo-metal relay/sequential catalysis is the third general strategy to access the enantioselective functionalization of allylic C-H bonds (Scheme 4c), wherein active allyl species generated from the Pd-catalyzed allylic C-H activation participate in the organocatalytic asymmetric transformation, leading to chiral allylic products.

Scheme 4 General modes for stereochemical control in the allylic C-H functionalization

After the asymmetric allylic C-H alkylation of allylarenes with enolizable aldehydes was established (Scheme 2), the concept was expanded to a similar reaction of 1,4-dienes (Scheme 5a).[12b] In both cases, the palladium complexes of triarylphosphines were the most efficient catalysts for allylic C-H activation in combination with chiral phosphoric acid to generate chiral π-allyl-Pd phosphate intermediates that could couple with enamines formed from achiral primary amine and aldehydes via transition state**TS-2** , in which the phosphate anion was supposed to provide a chiral environment for the stereoselective C-C bond-forming event. The design of the chiral catalyst for enantioselective allylic C-H alkylation of pyrazol-5-ones with allylarenes got inspiration from the allylic alkylation between pyrazol-5-ones and allylic alcohols enabled by Pd/phosphoric acid cooperative catalysis (Scheme 5b).[20] As a consequence, the combination of chiral phosphoramidite-Pd catalyst and chiral phosphoric acid allowed the allylic C-H alkylation reaction to proceed via the transition state (**TS-3**) and offered the highest enantioselectivity.[21]

Scheme 5 Enantioinduction via organo-metal cooperative catalysis

Apart from organo-metal cooperative catalysis, organo-metal relay catalysis[22] was also viable for realizing asymmetric allylic C-H functionalization (Scheme 6). In 2015, we described a highly diastereoselective carbonyl allylation of aldehydes with α-olefins,[23] proceeding via a sequential process consisting of a Pd-catalyzed oxidative allylic C-H borylation and a Brønsted acid-catalyzed allylboration of aldehydes. The use

of chiral phosphoric acid as co-catalyst offered the desired allylation product with 67% ee. In addition, the relay catalysis of chiral bifunctional squaramide and palladium complex enabled an asymmetric [2+2+1] annulation reaction of allyl ketones, barbituric acids and nitroalkenes[24] to generate highly functionalized cyclopentanes with high levels of stereoselectivities. Mechanistic studies suggested that chiral squaramide catalyst engaged in both the initial intermolecular and the final intramolecular Michael addition steps to enhance the enantioselectivity by kinetic resolution.

Scheme 6 Organo-metal relay catalytic reactions involving allylic C-H functionalization

To address incompatibility issues encountered in organo/metal relay catalysis, sequential catalysis[25] was introduced to fulfil asymmetric allylic C-H functionalization processes (Scheme 7). In the presence of chiral bis(pinanediolato)diboron reagent, Pd-catalyzed oxidative allylic C-H borylation of allylarenes furnished a chiral allylboronate intermediate,[26] which sequentially underwent chiral phosphoric acid-catalyzed allylboration of aldehydes to give homoallylic alcohols with excellent levels of stereoselectivity (Scheme 7a). In particular, the extension of such relay catalysis concept to allyl ethers met with great success.[27] The sequential catalysis of platinum complex and bifunctional chiral urea catalyst[17b]could work in similar manner to drive a one-pot process of asymmetric Michael addition and allylic C–H alkylation, leading to chiral tetrahydropyrans (Scheme 7b).

Scheme 7 Organo-metal sequentially catalyzed reactions involving allylic C-H functionalization

Even though organo-palladium combined catalysis has afforded a variety of asymmetric allylic C-H functionalization reactions, this strategy is seemingly workable for a limited number of nucleophiles presumably due to the incompatibility between the conditions of organocatalysis and allylic C-H activation. As such, chiral ligands have been continuously prepared and evaluated for the establishment of asymmetric allylic substitution reactions.[1b] In 2015, we accomplished a Pd-catalyzed enantioselective intramolecular allylic C-H oxidation by using BINOL-based bulky chiral phosphoramidites as ligands, allowing rapid synthesis of chiral chromans with high levels of stereoselectivity (Scheme 8).[28] In addition, chiral phosphoramidite-palladium catalysis was also viable for promoting asymmetric intramolecular allylic C-H amination reactions to build chiral tetrahydroquinazoline scaffolds (Scheme 8).[29] For 1,4-dienes bearing an additional arylethene-1-sulfonyl moiety, a sequential process consisting of enantioselective intramolecular allylic C-H amination and Diels-Alder reaction resulted in the formation of chiral fused tricyclic tetrahydropyrimidines. Furthermore, Pd-catalyzed intermolecular asymmetric allylic C-H alkylation of 1,4-dienes could be achieved by using a chiral phosphoramidite ligand (Scheme 8).[30] In addition, either 5-alkylthiazol-4(5H)-ones or cyclic β-ketoesters smoothly gave linear allylic alkylation products with high levels of enantioselectivity.

Scheme 8 Enantioselectivity induced by chiral phosphoramidite ligands

4. Regioselection Control

In Pd-catalyzed allylic substitution reactions with soft nucleophiles, the bond-forming event basically occurs via the outer-sphere nucleophilic addition to the η^3-allylpalladium intermediate.[1c] The regioselectivity is mainly controlled by the steric hindrance of the allyl moiety and thus, the terminal carbon of monosubstituted allyl substrates is preferentially attacked by nucleophiles to give the linear products (Scheme 9a). In sharp contrast, the branch- and enantioselective allylic substitution reactions are much more difficult to access by palladium catalysis. To date, only a few examples have been reported to preferentially give branched allyl products by tuning ligands to induce S_N1-type characteristics of allylpalladium species.[31] With regard to chiral phosphoramidite ligands, the typical behavior of mono-ligation to Pd offers the binding site for a suitable nucleophile,[32] thus opening the possibility of forming the branched product via an inner-sphere S_N2'-pathway[33] (Scheme 9b).

Scheme 9 Correlation between regioselection and ligand

Our efforts toward the control of regioselectivity started from understanding how the nucleophile-dependent regioselective allylic C-H alkylation of 1,4-dienes worked (Scheme 10). Through the screening of chiral

phosphoramidite ligands and reaction conditions, pyrazol-5-ones[21] and 5-alkylthiazol-4(5H)-ones[30a] preferred to afford chiral C5-branched and *E* -dienyl products, while azlactones,[17a] glycine Schiff bases[34] and α-angelica lactones[35] tended to give thermodynamically unfavorable chiral C5-branched and *Z* -dienyl products. Computational studies suggested that the *E/Z* - and regioselectivities were governed by the geometry and coordination pattern of nucleophiles.[17a] Comparing the two competing transition states **TS-4** and **TS-5** , both were able to provide the branched products via an S_N2'-pathway, but the former showed a more stable but longer vinyl π-allyl-Pd fragment (4.9 Å *vs* 4.5 Å), therefore, the*E/Z* -selectivity was conquered by the geometric match of the vinyl π-allyl-Pd fragment, the geometry of the nucleophile and the distortion of Pd-nucleophile bonding. With the use of 2-acylimidazoles or coordinating α-aryl carbonyls as nucleophiles, 1,4-dienes,[36] allyl ethers[37] and N-allylimines[38] all performed well to generate branched products with high levels of regio- and enantioselectivity. Recently, by using α-benzothiazylacetamides and α-heteroaryl ketones as nucleophiles, we established a branch- and enantioselective allylic C–H alkylation capable of accommodating diverse types of α-alkenes, ranging from 1,4-dienes and allylarenes to unactivated α-alkenes tethering a wide scope of appended functionalities.[39] Apart from carbon-carbon bond formation, the inner-sphere pathway was also amenable for the branch- and enantioselective construction of carbon-nitrogen bond via the direct coupling of allylic C-H bonds and aniline, albeit with only moderate enantioselectivity (Scheme 9).[40]

Scheme 10 Branch- and enantioselective allylic C–H alkylation

5. Applications

Pd-catalyzed asymmetric allylic C-H functionalization reactions provide a straightforward approach to access optically active starting materials or synthetically useful building blocks (Scheme 11). Starting with the asymmetric intramolecular allylic C-H oxidation, chiral chroman skeletons were smoothly given to allow the enantioselective syntheses of (+)-diversonol,[28] gonytolide C[41] and ascherxanthone A.[42] In addition, asymmetric intramolecular allylic C-H amination is able to provide chiral tetrahydroquinazolines that can serve as key intermediates for the synthesis of highly enantioenriched letermovir.[29] Furthermore, regio- and stereoselective allylic C-H alkylation reactions generate a range of key building blocks to access natural products, e.g. lepadiformine marine alkaloids,[17a]tanikolide[30b] and aigialmycin D,[27] and biologically important unnatural molecules, e.g. focalin,[38] tachykinin receptor antagonist[37] and Taniguchi lactone.[39]

Scheme 11 Applications of asymmetric allylic C–H functionalization reactions to the synthesis of natural products and bioactive substances

6. Conclusions

Over the past decade, Pd-catalyzed asymmetric allylic C-H functionalization has shown great potential as a general platform to access densely functionalized chiral molecules from easily available alkenes. In this essay, we briefly present our journey to the development of asymmetric catalytic systems, the mechanism of allylic C-H activation, the control of stereo- and regioselectivity, and the applications in asymmetric synthesis of natural products and bioactive substances. The use of asymmetric organo/palladium combined catalysis and the development of a library of structurally tunable and bulky chiral phosphoramidite ligands have opened new avenues to create regio- and enantioselective Pd-catalyzed allylic C-H functionalization reactions. The palladium complex of a phosphorus ligand and*p* -quinone oxidant turns out to be an active catalyst and allows the cleavage of the allylic C-H bond via an unprecedented concerted proton and two-electron transfer process. Experimental and computational studies have shown that the high levels of stereo- and branch-selectivity are not only governed by the coordination pattern of nucleophiles, but also regulated by the monoligation of chiral phosphoramidite ligands to allow for a nucleophile-coordination enabled inner-sphere S_N2'-pathway. The Pd-catalyzed asymmetric allylic C-H functionalization reactions are applicable to the rapid access of synthetically useful building blocks, enabling the asymmetric synthesis of a range of natural products and biologically active molecules. Notably, the strategies and concepts presented here for cleaving allylic C-H bonds and controlling selectivity are generally applicable. Hopefully, this essay will provide some inspiration for the rational design of new asymmetric allylic C-H functionalization transformations and prompt future

ground-breaking discoveries in this field.

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Pd-Catalyzed Asymmetric Allylic C-H Functionalization Pu-Sheng Wang, Liu-Zhu Gong* *Chin. J. Chem.* **2023**, *4*
This essay presents recent advances in Pd-catalyzed asymmetric allylic C-H functionalization in our lab, including the devel